IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Frank Karlsen, et al. Art Unit 1631
Serial No. 10/533,479
Filed April 29, 2005
Confirmation No. 4058
Title: A MICROFABRICATED FLUIDIC DEVICE FOR FRAGMENTATION
Examiner Russell Scott Negin

APPEAL BRIEF

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APPEAL BRIEF

This is an appeal from the final rejection of the claims of the above-referenced application made in the final Office action dated January 6, 2010. A Notice of Appeal was filed on July 6, 2010.

The appeal brief fee in the amount of $540 is submitted herewith.

I. REAL PARTY IN INTEREST

The real party in interest in connection with the present appeal is Norchip AS, owner of a 100 percent interest in the pending application.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any pending appeals or interferences which may directly affect or be directly affected by, or have a bearing on, the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The following is a statement of the status of all claims:

Claims 40, 42-54 and 56-77 remain pending. Claims 41 and 55 have been withdrawn from consideration.

A copy of the pending claims may be found in the CLAIMS APPENDIX submitted herewith.

Claims 40, 42-54 and 56-77 stand rejected under 35 U.S.C. §103(a) as follows:

#1. Claims 40, 43-50, 56-63, 69, 71-74, and 76 are rejected over the four-reference combination of Goodey et al., Fogler, Costa et al., and Levesque et al.

#2. Claim 42 is rejected over the five-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., and Feichtinger.

#3. Claims 51-53, 70 and 75 are rejected over the five-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., and Cottingham et al.

#4. Claim 54 is rejected over the six-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., Cottingham et al., and Raghu et al.

#5. Claims 64 and 66 are rejected over the five-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., and Sprague et al.

#6. Claims 65 and 67-68 are rejected over the six-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., Sprague et al., and Corominas.

#7. Claim 77 is rejected over the five-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., and Pfahler.

The rejections of all of claims 40, 42-54 and 56-77, i.e., all rejections #1 through #7, are being appealed.

IV. STATUS OF AMENDMENTS

No amendments have been filed after Final Rejection other than to correct the claim identifiers of claims 41 and 55, which have been entered as noted in the July 14, 2010 Advisory Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

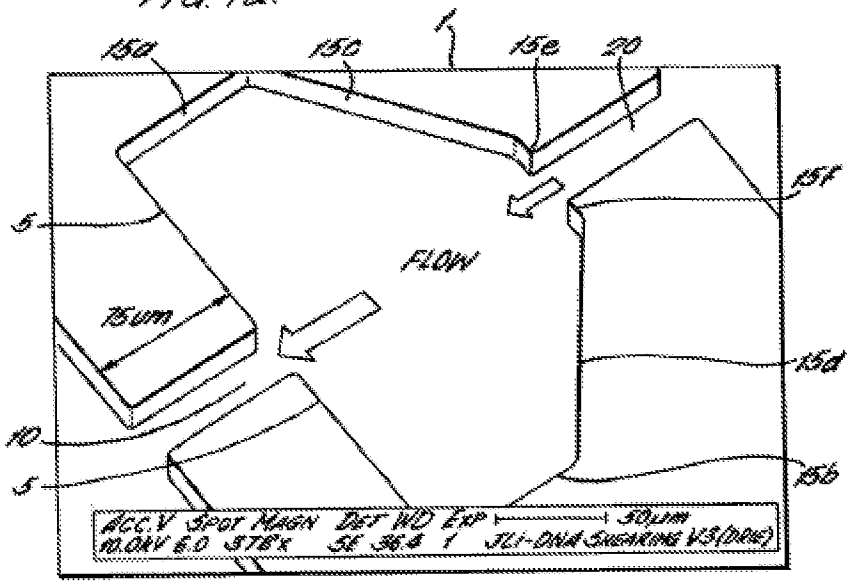
The following concisely explains the claimed subject matter, referring to the specification by paragraph number of the published application, U.S. 2006/0057581. It correlates claim elements to specific embodiments described in the application specification, but does not in any manner limit claim interpretation. Rather, the following

summary is provided only to facilitate the Board's understanding of the subject matter of this appeal.

Claim 40 is directed to a microfabricated device for fragmenting nucleic acids present in a fluid sample. The claim requires the device to have these elements, which are described in 0072-0073 and illustrated in Fig. 1a at the stated reference numeral:

Claim element	Fig. 1a
• a fragmentation cell	1
• an inlet port	20
• an outlet port	10
• a fragmentation cell bottom wall in which is formed the outlet port:	5
• a fragmentation cell top wall in which the inlet port is formed	15e, f
• side walls which extend from the top wall to the bottom wall	15a, c, b, d

FIG. 1a.



The claim also requires that the side walls taper inwardly as shown, e.g., at 15c, 15d to meet the *inlet* port. The bottom wall 5 is generally perpendicular to the direction of flow of fluid through the outlet port, as illustrated by an arrow. And the outlet port 10 is dimensioned to impede the flow of a fluid sample out of the cell so as to effect shearing of nucleic acids molecules.

Claim 40 requires that the device be microfabricated, which is a term well understood in the art, as further explained in paragraph 0004 by way of example:

> By the term microfabricated device or system as used herein is meant any device manufactured using processes that are typically, but not exclusively, used for batch production of semiconductor microelectronic devices, and in recent years, for the production of semiconductor micromechanical devices. Such microfabrication technologies include, for example, epitaxial growth (eg vapour phase, liquid phase, molecular beam, metal organic chemical vapour deposition), lithography (eg photo-, electron beam-, x-ray, ion beam-), etching (eg chemical, gas phase, plasma), electrodeposition, sputtering, diffusion doping and ion implantation. Although non-crystalline materials such as glass may be used, microfabricated devices are typically formed on crystalline semiconductor substrates such as silicon or gallium arsenide, with the advantage that electronic circuitry may be integrated into the system by the use of conventional integrated circuit fabrication techniques. Combinations of a microfabricated component with one or more other elements such as a glass plate or a complementary microfabricated element are frequently used and intended to fall within the scope of the term microfabricated used herein. Also intended to fall within the scope of the term microfabricated are polymeric replicas made from, for example, a crystalline semiconductor substrate.

Claim 71 is directed to an apparatus for sample analysis which "compris[es] a device as defined in claim 40."

Claim 72 is directed to an assay kit which "compris[es] a device as defined in claim 40."

Claim 74 is also defined by the structure in claim 40, being a process for fragmenting nucleic acids by pumping a fluid sample through the device in claim 40.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue presented on appeal is whether the subject matter of claims 40, 42-54 and 56-77 satisfies the requirements of 35 U.S.C. §103(a).

Claims 40, 43-50, 56-63, 69, 71-74, and 76 stand rejected over the four-reference combination of

a) Goodey et al., Journal o fthe American Chemical Society, volume 123, 2001, pages 2559-2570;

b) Fogler, Elements of Chemical Reaction Engineering, 2d Ed., New Jersey, Prentice Hall, 1992, pages 270-273;

c) Costa et al., US Pat. 5,545,529; and

d) Levesque et al., Journal of Biomechanical Engineering, 1985, Vol. 107, pages 341-347.

Appellants appeal this rejection.

Claim 42 is rejected over the five-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., and Feichtinger, US Pat. 3,356,489. Appellants appeal this rejection.

Claims 51-53, 70 and 75 are rejected over the five-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., and Cottingham et al., US Pat. 5,783,148. Appellants appeal this rejection.

Claim 54 is rejected over the six-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., Cottingham et al., and Raghu et al., US Pat. 5,853,624. Appellants appeal this rejection.

Claims 64 and 66 are rejected over the five-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., and Sprague et al., Circulation, volume 3, pages 648-656, 1987. Appellants appeal this rejection.

Claims 65 and 67-68 are rejected over the six-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., Sprague et al., and Corominas, US Pub. 2003/0089655. Appellants appeal this rejection.

Claim 77 is rejected over the five-reference combination of Goodey et al., Fogler, Costa et al., Levesque et al., and Pfahler, Doctoral Dissertation, Liquid Transport in Micron and Submicron Size Channels, U. of Penn., 1992. Appellants appeal this rejection.

VII. ARGUMENT

For purposes of this appeal, the claims are divided into two groups:

Group I: claims 40, 42-54 and 56-76

Group II: claim 77

A. Group I: claims 40, 42-54 and 56-76

A primary basis for this appeal is that the cited references are non-analogous art. First and foremost, a reference may only be relied upon in an obviousness rejection if the reference is analogous art to the application at issue. According to MPEP §2141.01(a):

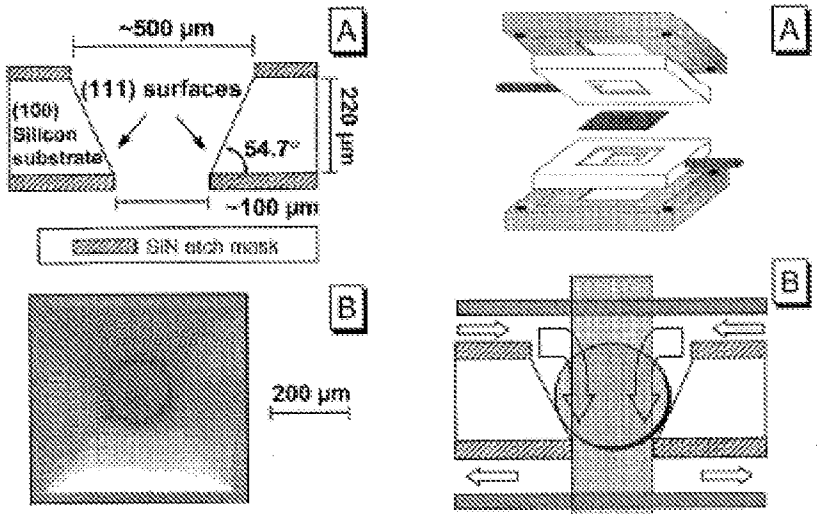
> **I. TO RELY ON A REFERENCE UNDER 35 U.S.C. 103, IT MUST BE ANALOGOUS PRIOR ART**
>
> The examiner must determine what is "analogous prior art" for the purpose of analyzing the obviousness of the subject matter at issue. "Under the correct analysis, any need or problem known in the field of endeavor at the time of the invention and addressed by the patent [or application at issue] can provide a reason for combining the elements in the manner claimed. " *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). Thus a reference in a field different from that of applicant's endeavor may be reasonably pertinent if it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his or her invention as a whole.
>
> In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

Applicants' field of endeavor is microfabricated devices for fragmentation of nucleic acids. The particular problem with which applicants were concerned was mechanically fragmenting nucleic acids.

More particularly, reference to the present application clearly indicates the field of endeavor of applicants' invention is microfabricated devices for fragmentation of nucleic acids. The title of the present application is "A Microfabricated Fluidic Device for

Fragmentation." As stated in sentence 1, lines 1 and 2 of paragraph 0001, "The present invention relates to a microfluidic device for nucleic acid fragmentation." The application goes on to explain the background purposes for fragmentation of DNA and RNA. See, e.g., paragraphs 0002 and 0003. The application also specifically explains the structure of the device as being microfabricated. See, e.g., paragraph 0004. All of the embodiments described in the application show microfabricated devices relating to fragmentation of nucleic acids. The preamble of claim 40 recites a "microfabricated device for fragmenting nucleic acids." The structure of applicants' claimed invention is clearly microfabricated, and the function of applicants' invention is clearly to fragment nucleic acids. Therefore, the field of applicants' invention is microfabricated devices for fragmentation of nucleic acids. Not one of the cited references is in this field.

With respect to the primary Goodey et al. reference, its field of endeavor of is analysis of complex fluids using multianalyte sensor arrays. This is not the same field as microfabricated devices for fragmenting nucleic acids, nor is it related to the field of microfabricated devices for fragmenting nucleic acids. According to Goodey et al.'s title, the reference is directed to "Development of Multianalyte Sensor Arrays Composed of Chemically Derivatized Polymeric Microspheres Localized in Micromachined Cavities." Goodey et al.'s descriptions such as the "Abstract," "Introduction," "Materials," "Fabrication of the Micrbead Arrays," and "Results and Discussion," make it clear that the structure of their sensor arrays, as shown in Figs. 1 and 2 of page 2563, includes microspheres immobilized or confined in a pyramidal "pit" having side walls that taper inward *to the outlet* of the pit so that the top-to-bottom flow direction of fluid to be analyzed forces the beads to the lower region of the pit, which serves as a self-centering aid:



See, e.g., page 2563, bottom column 2. The function of Goodey et al. is to include several of these microspheres immobilized in pits on a "taste chip" to provide a "chip-based system suitable for the analysis of complex fluids" via "solution-phase multianalyte detection." Page 2562, middle column 2. Thus, the field of endeavor of Goodey et al. is analysis of complex fluids using multianalyte sensor arrays. Goodey et al. flows complex fluids such as beverages and biological samples over a microbead sensor array for analysis of pH, metal cations, sugars, and antibodies within the fluids. See page 2560, bottom column 2. There is no suggestion of any shearing. Goodey et al. in no way disclose a reactor system for shearing polymers.

Moreover, addressing the second prong of the *Oetiker* analysis, Goodey et al. is also wholly unrelated to any particular problem with which applicants were concerned. The case law provides guidelines for determining the reasonable pertinence of a reference to the problem with which the inventor was concerned. According to the Federal Circuit, "the purposes of both the invention and the prior art are important in determining whether the reference is reasonably pertinent to the problem the invention attempts to solve." *In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992). If a reference is directed to a different purpose, the inventor would not have considered it. Id.

In *Clay*, for example, the Sydansk reference addressed the problem of recovering oil from rock, a matrix of porous, permeable sedimentary subterranean

formation. Id. The purpose of Sydansk's gel treatment of underground formations was to "fill anomalies so as to improve flow profiles and sweep efficiencies of injection and production fluids through a formation, while Clay's gel function[ed] to displace liquid product from the dead volume of a storage tank." Id. The Federal Circuit determined Clay was concerned with the problem of "preventing loss of stored product to tank dead volume while preventing contamination of such a product." Id. at 659-60. The Federal Circuit reversed the Board because a "person having ordinary skill in the art would not reasonably have expected to solve the problem of dead volume in tanks for storing refined petroleum by considering a reference dealing with plugging underground formation anomalies." Id. at 660.

The particular problem applicants were concerned with was random fragmentation of nucleic acids by mechanical force. Paragraph 0002. The purpose of applicants' device is to provide fragmented nucleic acid samples for use in, for example, "a nucleic acid sequence amplification and detection process" for "nucleic acid analysis or genomic library generation." Paragraphs 0001 and 0002. Goodey et al. is directed to solving a vastly different problem compared to applicants' invention. Goodey et al. is directed to the problem of analyzing mulitanalyte mixtures to enable intelligent, rapid, and accurate decisions related to the chemical composition of solution-phase samples. Page 2560, middle column 2. The purpose of Goodey et al. is to provide an automated "total analysis system" that is "capable analysis of pH, metal cations, sugars, and antibodies within complex fluids such as beverages, and biological samples." Page 2560, bottom column 2. As Goodey et al. explain in detail:

> For many important medical, process control, environmental, food safety, and food/beverage processing applications, the identification of analytes that are difficult to volatize without decomposition is essential. For these areas, the need for a chemically diverse, solution-phase multianalyte detection system is acute. Here the challenges associated with distinguishing between subtle differences in common electrolytes (Na^+ vs K^+ and Mg^{2+} vs Ca^{2+}), small differences in acidity (citric acid vs lactic acid), slight changes in protein structures (influenza AA vs influenza B, and complex sugar isomers (glucose vs galactose) makes the development of chemically diverse solution multianalyte detection arrays a very complex issue.

Page 2560, middle column 1. Simply stated, a person having ordinary skill in the art would not reasonably have expected to solve the problem of accomplishing random fragmentation of nucleic acids by mechanical force by considering a reference dealing with multianalyte sensor arrays composed of chemically derivatized polymeric microspheres. The gap between the problems addressed by applicants' device and Goodey's sensor arrays is far greater than the gap between the problems faced in *Clay* -- dead volume in tanks for storing refined petroleum and plugging underground formation anomalies -- which the Federal Circuit determined required reversal of the Board. Goodey et al. is clearly unrelated to the particular problem with which applicants were concerned.

The second cited reference -- Fogler -- is also non-analogous art. Fogler's field of endeavor is catalytic or fluid-solid reactors. This is a completely different field from microfabricated devices for fragmentation of nucleic acids. The Office relies on Fogler's Fig. 6-16, which shows a perfectly mixed fluidized continuous-stirred tank reactor (CSTR):

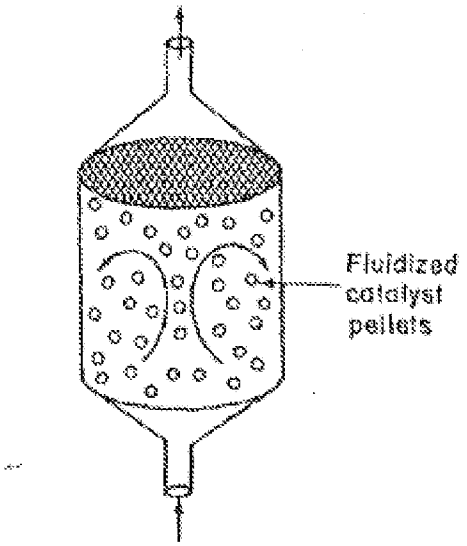


Figure 6-16 Fluidized CSTR reactor.

As is evident from the name "CSTR," the function of this reactor is to provide "perfect mixing behavior" to facilitate a catalyzed chemical reaction. See page 272. Regarding structure, CSTRs are of much larger scale than microfabrication devices. The field of

applicants' endeavor is *microfabricated* devices for fragmentation of nucleic acids. The function of applicants' invention is to mechanically fragment nucleic acids. Neither the function nor structure of the CSTR in Fogler is at all similar to the function or structure of applicants' microfabricated nucleic acid fragmenting device. In particular, the irrelevance of Fogler is underscored by the fact that applicants' device is microfabricated, as clearly explained in the specification in, for example, paragraph 0004, compared to the much larger scale of CSTRs. See, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 864-65 (Fed. Cir. 1993) (reversing a finding of obviousness based on non-analogous art where the reference at issue disclosed a "module [that] was developed for use in a controller of large industrial machinery and could not be used in a personal computer," for which the inventor's compact device was designed). The CSTR of Fogler is clearly outside the field of applicants' endeavor.

Moreover, the problem addressed by Fogler is unrelated to the particular problem faced by applicants. Fogler's CSTR addressed the problem of, for example, achieving continuous homogenous mixing to promote maximum fluid-to-solid contact to facilitate catalytic reactions. Applicants' particular problem was mechanically fragmenting amino acids. A person having ordinary skill in the art would not reasonably have expected to solve the problem of accomplishing fragmentation of nucleic acids by mechanical force by considering a reference dealing with facilitating fluid-solid chemical reactions. Therefore, Fogler is wholly unrelated to the particular problem with which applicants were concerned.

It is evident that the Office's thought process in citing Goodey et al. and Fogler was to locate a couple reactors having tapering side walls, and then distort their applicability as having relevance to microfabricated devices for fragmenting nucleic acids. In particular, on pages 10-11 of the final Office action, the Office has cast the fields as ridiculously broad: "Biotechnology/catalysts"; "Catalysts/reactions"; and "Biotechnology." The Office is not free to characterize any two structures as similar if they have just anything in common; is not free to characterize any two functions as similar if they have just anything in common; is not free to define field boundaries as broadly as necessary to cover both the invention and the art; and is not free to define a problem's boundaries as broadly as necessary to cover both applicants' and the prior

art's problems. For example, in *In re Clay*, Id., the Federal Circuit, in reversing the examiner, determined that it is unreasonable to characterize the fields of endeavor as broadly as "the petroleum industry" or even "maximizing withdrawal of petroleum stored in petroleum reserves." Rather, the court determined the applicant's field to be "*storage* of refined hydrocarbons" and the prior reference's field to be "*extraction* of crude petroleum," and rejected application of the cited Sydansk reference as non-analogous art.

In view of the foregoing, all of the rejections should be withdrawn because neither Goodey et al. nor Fogler are analogous prior art.

Based on the assertions on pages 10-11 of the final Office action on which the Office bases its conclusion that Goodey et al. is analogous art, it is evident the Office has misunderstood this reference. In particular, the Office states

> "Problem/Function: This [Goodey et al.] study demonstrates use of mechanical force to provide stress to polymer microspheres in order to produce microspheres with specific properties."
>
> "Consequently, all four references use shearing (i.e. a mechanical force) to achieve a desired resultant product. For Goodey et al., Levesque et al., and Costa et al., the shearing results in fragmented or elongated polymers (just like in the instantly rejected claims)."

This is incorrect. Goodey et al. purchased "off the shelf" microspheres, arranged them in a tray of cavities in microchips, and flowed fluid over them for analysis. The flow cell was positioned on top of a microscope for viewing:

Experimental Section

Materials. Polystyrene–poly(ethylene glycol) (PS–PEG) graft copolymer microspheres (~130 μm in diameter when dry and ~230 μm when hydrated) were purchased from Novabiochem. Normal amine activation substitution levels for these beads were between 0.2 and 0.4 mmol/g. Commercial-grade reagents were purchased from Aldrich and used without further purification except as indicated below. Fluorescein isothiocyanate was purchased from Molecular Probes. All solvents were purchased from EM Science, and those used for solid-phase syntheses were dried over molecular sieves. Methanol was distilled from magnesium turnings.

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The choice of the polystyrene–polyethylene (small molecule, anions, cations) and agarose (enzymes, proteins, antibodies) microspheres for these studies was based, in part, on the good optical transparency of these bead matrixes, the availability of microspheres with diameter values in the range of 120–350 μm, and their compatibility with the solvents of interest.[64] For both types of beads, the microspheres swell in size in a dramatic manner upon their exposure to organic and aqueous fluids. Under typical analysis conditions, ~85% of the internal environment of the microsphere is composed of solvent. A light cross-linking of the matrix backbone provides good mechanical properties to these systems as well as a restoring force that fosters the reversible exchange of solvents in to and out of the microspheres. Immobilizing the polymer beads within cavities in the chips allows for the full advantage of polymer swelling, while avoiding problems incurred by attaching the polymer to a platform. It should be appreciated that with the use of these microporous beads it is possible to utilize an effective sampling thickness of 250–350 μm. This long effective path length

combined with large flow rates (vide infra) has the potential to lower detection thresholds and increase measurement sensitivity for the microbead array methods relative to other array strategies that exploit monolayer films or thin polymeric pads.[16]

The sensor array chips are sealed within a customized flow cell designed to minimize exchange volume and allow optical measurements to be made, Figure 2A. The flow cell is essentially composed of two siloxane polymer layers that are held together by a two-piece aluminum casing. Solutions are typically introduced to the flow cell using a liquid chromatography system. Liquid samples can also be introduced into the cell using a syringe via a Luer lock connection. Top and bottom reservoirs are created with thin depressions in the siloxane layers. Source (top) and drain (bottom) layers that service the microbead array are connected to the delivery and exit tubing of the fluid delivery system. Using this type of fluid packaging method alongside liquid chromatography systems, it is possible to acquire rapidly concentration isotherms for a variety of analytes over broad sample ranges. Using the stated top-to-bottom flow direction, the beads become forced to the lower region of the cell and under these circumstances the pyramidal pits serve as self-centering aids, Figure 2B. Fluid flow rates of .....

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Accordingly, contrary to the Office's assertion, Goodey et al. do ***not*** demonstrate "use of mechanical force to provide stress to polymer microspheres in order to produce microspheres with specific properties." Goodey et al. do ***not*** "use shearing to achieve a desired resultant product." And in Goodey et al. there is ***not*** "shearing resulting in fragmented or elongated polymers (just like in the instantly rejected claims)." And examination of Goodey et al.'s "function" and "result" as encouraged by the Office in fact underscores that it is wholly non-analogous.

Applicants further respectfully submit that even if the art were analogous, there is no reason to make the proposed combination, and the proposed combination does not lead to the device of applicants' claim 40. Claim 40 has these express claim requirements:

a) a fragmentation cell, an inlet port, and an outlet port;

b) the outlet port is dimensioned to impede the flow of a fluid sample out of the cell so as to effect shearing of nucleic acids molecules;

c) a chamber of the fragmentation cell having a top wall in which is formed the inlet port, a bottom wall in which is formed the outlet port, and side walls; and

d) the side walls taper inwardly to meet the inlet port.

The express requirement that the sidewalls taper inwardly to meet the inlet port is described at length in the specification and is a critical feature of the invention:

The side walls portions next to or adjacent the inlet port advantageously subtend an angle of less than 90 degrees to the longitudinal axis of the inlet port. Such a gradual opening allows for substantially bubble-free filling of the cell.

Paragraph [0019] of published application 2006/0057581

FIG. 1 (a) shows a scanning electron micrograph (SEM) of a fragmentation cell 1 (or shearing unit), one in a connected series made by deep reactive-ion etching (DRIE) in silicon. The constriction outlet 10 (approx. 75 μm long) is designed to have an abrupt change in cross-section from large to small in the flow direction. ***At the chamber inlet 20, a gradual opening has been found to help avoid air bubbles being trapped in the structure.*** The constriction width (i.e. the width of the outlet and inlet) is approx. 25 μm and the feature depths approx. 50 μm.

Paragragh [0072] of published application 2006/0057581

The shape of fragmentation cell 1 may be described as an irregular hexagon with an essentially straight bottom wall 5 in which the outlet 10 is formed at approximately the mid point. It can be seen that the bottom wall 5 is substantially perpendicular to the longitudinal axis of the outlet 10 (and the direction of flow). Thus, the bottom wall 5 subtends an angle of approximately 90 degrees to the longitudinal axis of the outlet 10 (and the direction of flow). The bottom wall 5 is adjacent and substantially perpendicular to two lower side wall portions 15a and 15b. The upper portions 15c and 15d of the side walls taper inwardly to meet the inlet 20 at the top of the cell 1. ***Thus, upper side walls portions 15c and 15d***

> ***each subtend an angle of less than 90 degrees to the longitudinal axis of the inlet (and the direction of flow).*** It can be seen, however, that the uppermost side wall portions 15e and 15f immediately adjacent the inlet 20 subtend an angle of approximately 90 degrees to the longitudinal axis of the inlet 10 (and the direction of flow). It can also be seen that the cell 1 is asymmetric about the horizontal axis and substantially symmetric about the longitudinal axis (the longitudinal axis is essentially coincident with the direction of flow).
>
> Paragragh [0073] of published application 2006/0057581

Incorporating this tapering feature cannot fairly be deemed to have been obvious from the cited references or general knowledge in the art, even if these references were -- improperly -- deemed to be analogous art. For there to be obviousness, there must be articulated ***reasons*** why one skilled in the art would have selected the particular elements of Goodey et al., Fogler et al., Costa et al. and Levesque et al. and combined them in the manner proposed:

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398, 418 (2007)

ESTABLISHING A *PRIMA FACIE* CASE OF OBVIOUSNESS

> The key to supporting any rejection under 35 U.S.C. **103** ***is the clear articulation of the reason(s) why the claimed invention would have been obvious***. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. **103** should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, ***there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness***." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR,* 550 U.S. at ____, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval)(MPEP 2142, emphasis added).

The Office acknowledges that Goodey et al. do not disclose side walls tapering inwardly to meet the inlet port or the use of the device to shear nucleic acids. The

Office then asserts on page 8 of the action that it would have been obvious to modify Goodey et al.'s device with side walls tapering inwardly to meet the inlet port of Fogler. But not one of the three "reasons" recited by the Office on page 8 supports this conclusion.

Statement I. "It would have been obvious ... because it is obvious to substitute known elements in the prior art to yield a predictable result."

This statement is circular: "it is obvious ... because it is obvious." This is nothing more than a legal conclusion. This does not constitute "articulated reasoning" with "rational underpinning" which the MPEP and *KSR* decision emphasize the law requires. Indeed Goodey et al.'s reactor is a "known element"; and so are Fogler et al.'s "tapered walls." But here there is no basis upon which to predict any result of the proposed modification, much less any reason to make the proposed modification. Goodey et al.'s device is a "Multianalyte Sensor Array Composed of Chemically Derivatized Polymeric Microspheres" which was developed to assay "multifunctional fluids" (p. 2560, column 1), i.e., to figure out what a particular fluid contains. It is related to electronically analyzing the taste and smell of fluids (p. 2560, column 2). Fogler's device is a fluidized continuous-stirred tank reactor (CSTR) described on page 272 as "a catalytic or fluid-solid reactor." Fogler does not discuss what the purpose is for tapering toward the inlet, if any. Nor does Fogler discuss what the result is of tapering toward the inlet. There is simply no basis to conclude that there would be any predictable or desirable result achieved by modifying Goodey et al.'s taste analyzer with this feature of Fogler's stirred tank reactor. Not only does Fogler not state what results from his inlet tapering in his stirred tank reactor, but there is moreover no basis to predict what results such tapering would have on Goodey et al.'s taste analyzer. This is especially true considering what a disparate device Fogler's stirred tank reactor is from Goodey et al.'s taste analyzer. Accordingly, the Office's statement that "It would have been obvious . . . because it is obvious to substitute known elements in the prior art to yield a predictable result" provides zero support for the Office's conclusion of obviousness.

Statement II. "In this instance, the tapered reactor in Fogler is an alternative to the reactor in Goodey et al."

Any substitution is, of course, an "alternative," so this sentence does not add anything to the analysis. Most importantly, here the Office does not provide any reason why it would have been obvious to implement this alternative. That something is an alternative does not make it an obvious modification. Why is it a *practical* alternative? Why would one skilled in the art infer interchangeability? Fogler discloses a continuous stirred tank reactor. Goodey et al. discloses a device for analyzing taste/smells. There is no reason of record why tapers in CSTRs are known alternatives for anti-tapers at inlets in chambers of smell analyzers. And in fact there is no basis for concluding this significant of a feature from a stirred tank reactor would be a suitable alternative for the walls in Goodey et al.'s disparate taste/smell analyzer, which in fact taper in the directly opposite orientation at the inlet for the express purpose of forcing the beads against the outlet.

Statement III. "There would have been a reasonable expectation of success in combining Goodey et al. with Fogler because both are reactor systems used for manipulating polymers."

The fact that two things are reactor systems used for manipulating polymers does not mean that there would be any reasonable expectation of success. An assessment of whether there would be any reasonable expectation of success cannot be made in a vacuum. This inquiry only has meaning in the context of a particular goal and prospects for "success" of achieving that goal. Goodey et al.'s cited component is a chamber of a device for analyzing smells. There is no information given in the Office action as to what effect reversing the taper of the side walls at the inlet would have on the chamber's effectiveness in the smell-analyzing device. In fact, one would reasonably infer from Goodey et al.'s goal of forcing microbeads against the outlet that reversing the inlet taper would defeat this goal. So there is no basis for reaching any conclusion about the prospects for success.

Accordingly, all three of these statements which the Office advances as "reasons" to make the hindsight modification are conclusory statements, wholly devoid

of any explicit analysis, and contrary to technical reason. The Office does not state what predictable results the combination of Goodey et al. and Fogler would provide, nor does the Office state what success is reasonably expected by the combination. The statements of predictability, alternatives, and expectations are merely overly broad statements of relation. They are not *reasons* to combine. Applicants therefore respectfully submit that the Office's proposed "reasons" are not really "reasons" at all, and the rejection is deficient.

More important than the deficient analysis provided by the Office, however, is that it is in fact evident that no person having ordinary skill in the art and common sense would modify the chamber of Goodey et al. to have Fogler's side walls tapered to the inlet port. In fact, Goodey et al. teach away from such a configuration. Goodey et al. disclose side walls that taper inwardly to meet the outlet port, not to meet the inlet port. This configuration is provided for a specific and important reason. As explained above, the Goodey et al. reference is directed to flowing complex fluids such as beverages and biological samples over a microbead sensor array for analysis of pH, metal cations, sugars, and antibodies within the fluids. Goodey et al. emphasize the importance of "strategic placement" of the sensor, more specifically the microbead sensor or polymeric microsphere, for proper fluid flow over the sensor. As explained in the caption for Figure 2, there is shown a section of a "bead confinement strategy":

> Using the stated top-to-bottom flow direction, the beads become forced to the lower region of the cell and under these circumstances the pyramidal pits serve as self-centering aids. Goodey et al.; page 2563, bottom column 2.

Goodey et al. describe the beads as "immobilized" numerous times, e.g.:

> Immobilizing the polymer beads within the cavities in the chips allows for the full advantage of polymer swelling, while avoiding the problems incurred by attaching the polymer to a platform. Goodey et al. page 2563, col. 1

Modifying the cavity to have side walls tapered to the inlet port would cause turbulence tending to mobilize or unseat the sensors. This would render Goodey et al. inoperable for its intended purpose. As provided by MPEP §2143.10(V):

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

Nor is there any *KSR*-required *reason* to change the tapering in the Goodey et al. device, because to do so would disembowel it of its function and goal - to securedly seat the microbeads against the outlet. In *Gordon* -- which is on all fours with the present situation -- the Board had concluded that a claimed blood filter assembly would have been produced by simply turning the prior art oil strainer upside down. However, the Federal Circuit concluded that the proposed inversion would have rendered the prior art device inoperable, so that obviousness could not fairly be established on the basis the Board proposed. The Office's current proposal to invert Goodey et al.'s tapering is similarly unreasonable, inappropriate, and not sustainable.

In addition, to incorporate tapering toward Goodey et al.'s inlet would effectively decrease the opening of the cavity, which Goodey et al. explain "complicates the bead placement issue." Column 2, page 2562. Accordingly, a person having ordinary skill in the art would have no reason to modify and would in fact be discouraged from modifying Goodey et al. to incorporate Fogler's side walls tapered inward to the inlet port.

The Office further states that it "would have been obvious to modify devices of Goodey et al. and Fogler et al. by use of the cellular shearing device of Levesque et al. . . . because it is obvious to substitute known elements in the prior art to yield a predictable result." Again, this reasoning is circular and conclusory. Of course Levesque et al.'s elements are known and so are Goodey et al.'s. But whatever Levesque et al. disclose to accomplish shearing cannot fairly be deemed to have a predictable impact on Goodey et al.'s disparate taste/smell analyzer, which is not intended for shearing.

Moreover, the Office fails to explain how the combination of Goodey et al. and Fogler would be modified to incorporate the "cellular shearing device" of Levesque et al. As shown in Figure of page 341, the "cellular shearing device" of Levesque et al. is a chamber having parallel walls that result in steady, uniform laminar flow. The Office is suggesting that the combination of Goodey et al. and Fogler should be modified to have parallel walls, and the Office has impermissibly and conveniently selected individual elements without any respect for how they might mechanically impact Goodey et al.'s taste/smell analyzer. At best, this analysis is based on speculation and unfounded assumptions.

It is evident, in view of a) the disparate nature of the references, b) the failure of either of the primary two references to relate to any sort of fragmentation, and c) the Office's lack of explicit technical reasoning to support the proposed combinations, that the Office has applied impermissible hindsight in making this four-way combination using applicants' claims as a template. Goodey et al., Fogler, Levesque et al., and Costa et al. are wholly unrelated to each other:

> Goodey et al.'s isolating a fluid sample for electronic taste and smell analysis
>
> versus
>
> Fogler's chemical reaction vessel
>
> versus
>
> Levesque et al.'s study of hemodynamic forces on vascular endothelial cells
>
> versus
>
> Costa et al.'s assay for detecting covalent DNA-protein complexes.

There is absolutely no reason one skilled in the art would incorporate aspects from each of these disparate references of the four-way combination to arrive at the combination of elements explicitly required by claim 40. Moreover, the references teach away from this

combination. Claim 40 is therefore respectfully submitted to be patentable over this combination.

Claims 42-54 and 56-76 depend from claim 40, and were all rejected on the basis of Goodey et al., Fogler, Levesque et al., and Costa et al. These claims are therefore all patentable for the same reasons as claim 40.

B. Group II: claim 77

Claim 77 depends indirectly from claim 40, has all the requirements of claim 40, and stands rejected as obvious over the five-way combination of Goodey et al., Fogler, Levesque, Costa et al., and Pfahler. This claim is therefore patentable for the same reasons as stated above in connection with claim 40.

Claim 77 is further patentable in view of its express requirement that the outlet port has a constriction width is from 5 to 50 μm. The Office admits on page 20 of the Office action that the first four references do not teach this element. The Office then states on page 21 that the Pfahler dissertation studies liquid transportation in micron and submicron size channels, and illustrates on page 81 the 5 to 50 μm dimension. And indeed Pfahler shows 30 μm channel width.

The Office states on page 21 the basis for modifying the Goodey/Fogler/Levesque/Costa device is

> It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the nucleic acid fragmentation device of Goodey et al., Fogler, Levesque et al, and Costa et al. by use of the recited dimensioned constriction in Pfahler because it is obvious to substitute known elements in the prior art to yield a predictable result. In this instance, the narrower constriction on Pfahler provides an alternative form of constriction as in Goodey et al. There would have been a reasonable expectation of success in combining Pfahler with Goodey et al., Fogler, Levesque et al, and Costa et al. because all of the sources pertain to analogous reactor systems for analyzing polymers or biopolymers.

This statement is circular: "it is obvious ... because it is obvious." This is nothing more than a legal conclusion. This does not constitute "articulated reasoning" with "rational underpinning" which the MPEP and *KSR* decision emphasize the law requires. Indeed Goodey et al.'s reactor is a "known element"; and so are Fogler et al.'s "tapered

walls" and Pfahler's constriction size. But here there is no basis upon which to predict any result of the proposed modification, much less any reason to make the proposed modification. Goodey et al.'s device is a "Multianalyte Sensor Array Composed of Chemically Derivatized Polymeric Microspheres" which was developed to assay "multifunctional fluids" (p. 2560, column 1), i.e., to figure out what a particular fluid contains. It is related to electronically analyzing the taste and smell of fluids (p. 2560, column 2). Pfahler's device is silicon etched to create a shape for his doctoral study of "rheology and flow dynamics of Newtonian and non-Newtonian fluids in small uniform channels." (Pfahler - Abstract). There is simply no basis to conclude that there would be any predictable or desirable result achieved by modifying Goodey et al.'s taste analyzer with this feature of Pfahler's channels. There is moreover no basis to predict what results such tight constriction would have on Goodey et al.'s taste analyzer. This is especially true considering what a disparate device Pfahler's is from Goodey et al.'s taste analyzer. Accordingly, the Office's statement that "It would have been obvious . . . because it is obvious to substitute known elements in the prior art to yield a predictable result" provides zero support for the Office's conclusion of obviousness.

Furthermore, any substitution is, of course, an "alternative," so the Office's bald assertion of alternatives does not add anything to the analysis. Most importantly, here the Office does not provide any reason why it would have been obvious to implement this alternative. That something is an alternative does not make it an obvious modification. Why is it a *practical* alternative? Why would one skilled in the art infer interchangeability? And in fact there is no basis for concluding this significant of a constriction would be a suitable alternative for the walls in Goodey et al.'s disparate taste/smell analyzer.

Furthermore, the fact that two devices are, as the Office characterizes them, reactor systems used for manipulating polymers or biopolymers does not mean that there would be any reasonable expectation of success. An assessment of whether there would be any reasonable expectation of success cannot be made in a vacuum. This inquiry only has meaning in the context of a particular goal and prospects for "success" of achieving that goal. Goodey et al.'s cited component is a chamber of a device for analyzing smells. There is no information given in the Office action as to

what effect shrinking the outlet stricture to 50 microns would have on the chamber's effectiveness in the smell-analyzing device. So there is no basis for reaching any conclusion about the prospects for success.

In view of the foregoing, applicants respectfully request reversal of the rejection of claim 77.

CONCLUSION

In view of the foregoing, appellants respectfully request that the Office's rejections of claims 40, 42-54 and 56-77 be reversed and that the pending claims be allowed.

Respectfully Submitted,

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VIII. CLAIMS APPENDIX

1. - 39. (Canceled)

40. (Previously presented) A microfabricated device for fragmenting nucleic acids present in a fluid sample, the device comprising an inlet port, a fragmentation cell, and an outlet port downstream from said inlet port, said cell being in fluid communication with said ports, and wherein said outlet port is dimensioned to impede the flow of a fluid sample out of said cell so as to effect shearing of nucleic acids molecules therein, wherein the fragmentation cell comprises a chamber having a bottom wall in which is formed the outlet port, the bottom wall being generally perpendicular to the direction of flow of fluid through the outlet port, and wherein the fragmentation cell has a top wall in which the inlet port is formed, and side walls which extend from the top wall to the bottom wall, and wherein the side walls taper inwardly to meet the inlet port.

41. (Withdrawn) A microfabricated device as claimed in claim 40, wherein the fragmentation cell has the shape of an irregular polygon, preferably an irregular hexagon, with an essentially straight bottom wall in which the outlet port is formed at approximately the mid point, and wherein the bottom wall is substantially perpendicular to the longitudinal axis of the outlet port.

42. (Previously presented) A microfabricated device as claimed in claim 40, wherein the fragmentation cell is generally pear shaped with an essentially straight bottom wall in which the outlet port is formed at approximately the mid point, the bottom wall being substantially perpendicular to the longitudinal axis of the outlet, and wherein the bottom wall is connected by curved walls to side walls, which converge or taper inwardly to meet the inlet port.

43. (Previously presented) A microfabricated device as claimed in claim 40, wherein the width of the fragmentation cell abruptly decreases at the outlet port.

44. (Previously presented) A microfabricated device as claimed in claim 40, wherein the outlet port comprises a constriction having a width in the range of from 1 to 100 μm.

45. (Previously presented) A microfabricated device as claimed in claim 40, wherein the outlet port is formed in approximately the middle of the bottom wall.

46. (Previously presented) A microfabricated device as claimed in claim 40, wherein the side walls taper inwardly to meet the outlet port.

47. (Previously presented) A microfabricated device as claimed in claim 40, wherein the bottom wall is adjacent and substantially perpendicular to two lower side wall portions.

48. (Previously presented) A microfabricated device as claimed in claim 47, wherein the upper portions of the side walls taper inwardly to meet the inlet port.

49. (Previously presented) A microfabricated device as claimed in claim 40, wherein side walls or portions thereof next to or adjacent the inlet port subtend an angle of less than 90 degrees to the longitudinal axis of the inlet port.

50. (Previously presented) A microfabricated device as claimed in claim 40, wherein the fragmentation cell comprises a bottom wall in which the outlet port is formed at approximately the mid point, the bottom wall being substantially perpendicular to the longitudinal axis of the outlet, and side walls which converge or taper inwardly to meet the inlet port.

51. (Previously presented) A microfabricated device as claimed in claim 40, wherein the device further comprises an obstacle located in the cell in the direct path between the inlet and outlet ports.

52. (Previously presented) A microfabricated device as claimed in claim 51, wherein the space between sides of the obstacle and sides of the cell defines a bifurcated path for the fluid sample.

53. (Previously presented) A microfabricated device as claimed in claim 51, wherein the obstacle is shaped so that the flow path of a fluid sample in a region adjacent the outlet port is substantially perpendicular to the longitudinal axis of the outlet.

54. (Previously presented) A microfabricated device as claimed in claim 51, wherein the obstacle is in the form of a generally triangular obstacle, with its three sides substantially parallel to the bottom wall and side walls of the cell, the space between the sides of the obstacle and the sides of the cell defining a bifurcated path for the fluid sample.

55. (Withdrawn) A microfabricated device as claimed in claim 40, wherein the fragmentation cell is asymmetric about the horizontal axis and substantially symmetric about the longitudinal axis, the longitudinal axis being essentially coincident with the direction of flow.

56. (Previously presented) A microfabricated device as claimed in claim 40, further comprising an access channel in fluid communication with the inlet port.

57. (Previously presented) A microfabricated device as claimed in claim 40, further comprising collection means in fluid communication with the outlet port.

58. (Previously presented) A microfabricated device as claimed in claim 40, further comprising means for effecting flow of a sample into the inlet port, through the fragmentation cell and out of the outlet port.

59. (Previously presented) A microfabricated device as claimed in claim 58, wherein said means for effecting flow comprises one or more pumps.

60. (Previously presented) A microfabricated device as claimed in claim 58, wherein said means for effecting flow comprises one or more variable volume chambers in communication with the inlet port and/or outlet port, wherein altering the volume of the variable volume chamber(s) effects and/or restricts flow of a fluid sample into and/or out of the fragmentation cell.

61. (Previously presented) A microfabricated device as claimed in claim 40 which comprises a substrate and an overlying cover, the fragmentation cell being defined by a recess in a surface of the substrate and the adjacent surface of the cover.

62. (Previously presented) A microfabricated device as claimed in claim 61, wherein the substrate is formed from silicon and the overlying cover from glass.

63. (Previously presented) A microfabricated device as claimed in claim 62, wherein the glass cover is anodically bonded to the silicon substrate.

64. (Previously presented) A microfabricated device as claimed in claim 40 which comprises at least first and second fragmentation cells, the outlet port of the first cell being in fluid communication with the inlet port of the second cell.

65. (Previously presented) A microfabricated device as claimed in claim 64, further comprising a third fragmentation cell, the outlet port of the second cell being in fluid communication with the inlet port of the third cell.

66. (Previously presented) A microfabricated device as claimed in claim 64 comprising a plurality of serially connected fragmentation cells.

67. (Previously presented) A microfabricated device as claimed in claim 64, wherein the size of the outlet port decreases the further down stream the fragmentation cell.

68. (Previously presented) A microfabricated device as claimed in claim 67, wherein the size of the outlet port gradually decreases from the first fragmentation cell to the last fragmentation cell downstream.

69. (Previously presented) A microfabricated device as claimed in claim 40 for fragmenting nucleic acids present in a biological fluid, a dairy product, an environmental fluid or drinking water.

70. (Previously presented) A microfabricated reaction chamber system for carrying out a nucleic acid sequence amplification and detection process on a nucleic acid sample, the system comprising a microfabricated device as defined in claim 40.

71. (Previously presented) An apparatus for the analysis of biological and/or environmental samples, the apparatus comprising a device as defined in claim 40.

72. (Previously presented) An assay kit for the analysis of biological and/or environmental samples, the kit comprising a device as defined in claim 40 and means for contacting the sample with the device.

73. (Previously presented) An apparatus as claimed in claim 71 which is disposable.

74. (Previously presented) A process for fragmenting nucleic acids present in a fluid sample, the process comprising:

(a) providing a device as defined in claim 40;

(b) providing a fluid sample comprising nucleic acids;

(c) pumping the fluid sample into the inlet port of said device, through the fragmentation cell and out of the outlet port; and

(d) collecting the thus fragmented sample at the outlet port.

75. (Previously presented) A process as claimed in claim 74 which further involves a nucleic acid sequence amplification and detection process on the fragmented nucleic acid sample.

76. (Previously presented) The microfabricated device as claimed in claim 62, wherein the glass cover is anodically bonded to the silicon substrate optionally through an intermediate silicon oxide layer formed on the surface of the substrate.

77. (Previously presented) The microfabricated device as claimed in claim 44 wherein the constriction width is from 5 to 50 μm.

IX. RELATED PROCEEDINGS APPENDIX

Not applicable.

X. EVIDENCE APPENDIX

Not applicable.